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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 26 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Peter E. Voytek, Ph.D.
Manager, HAP Task Force
2001 L Street, NW
Suite 506A
Washington, DC 20036

Dear Dr. Voytek:

EPA has reviewed the two alternative PK testing proposals submitted by the HAP Task Force on November 22, 1996. These proposals are entitled "Proposal for Pharmacokinetics Study of Ethylene Dichloride" and "Proposal for Pharmacokinetics Study of 1,1,2-Trichloroethane."

These proposals were prepared in response to EPA's invitation for proposals for pharmacokinetics (PK) studies for the hazardous air pollutants (HAPs) listed in the proposed test rule for HAPs (61 FR 33178; June 26, 1996). The PK studies would be used to inform the Agency about route-to-route extrapolation of toxicity data from routes other than inhalation when it is scientifically defensible in order to empirically derive the inhalation risk. The PK proposals could form the basis for negotiation of enforceable consent agreements (ECAs) that would provide for testing in lieu of some or all of the tests proposed in the HAPs rule.

The following provides a background to EPA's method of evaluating the proposed PK strategies. As you recall, in the preamble to the proposed test rule, EPA indicated that, when reviewing PK proposals, it would use the Gerrity and Henry (1990) decision tree as an element in evaluating the proposed PK studies. The Agency also indicated that it would use mechanistic data in determining the appropriateness of route-to-route extrapolation of the existing data base as an alternative to conducting some or all of the testing required under the proposed HAPs test rule. Pharmacokinetics and mechanistic data may be used to inform the Agency about route-to-route extrapolation when EPA determines that extrapolation from existing studies may provide sufficient data to substitute for required testing under the proposed rule. Pharmacokinetics and mechanistic data alone may not be used to substitute for proposed required testing when studies by a route other than inhalation do not exist or are deemed by EPA to be inadequate. In such cases, however, pharmacokinetics and mechanistic data may be used to support a decision that required testing could be conducted using routes other than inhalation.

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EPA has concluded that the strategies described in the proposals for ethylene dichloride (EDC) and 1,1,2-trichloroethane (TCE) offer sufficient technical merit to warrant further consideration. The Agency invites the HAP Task Force to consider EPA's preliminary technical analyses of these proposals, copies of which are enclosed in this letter. Please note that these analyses, including all discussions concerning data adequacy and test procedures/methods pertain only to the adequacy of PK proposal for its intended purpose and not to the statutory basis for issuing the HAPs rule under section 4 of the Toxic Substances Control Act (TSCA).

If, after the HAP Task Force has had the opportunity to review these analyses, you have a continued interest in pursuing the ECA process for either or both chemicals as an activity distinct from the test rule process, please respond to me in writing by July 31, 1997. Depending on the Panel's response, EPA will determine whether or not to proceed with the ECA process for either or both chemicals. (The procedures for ECA negotiations are described at 40 CFR 790.22(b).) Under this process, EPA would publish a notice in the Federal Register soliciting interested parties to participate in or monitor negotiations for an ECA on EDC and TCE. The notice will also announce a date for a public meeting to negotiate the ECA. At these negotiations EPA may raise issues, based on the Agency's further review of the proposed strategy, that differ from those contained in the preliminary technical analysis. EPA notes that, as a result of unexpected complexities arising in the review of the proposals and contrary to the statement in the preamble to the proposed HAPs test rule, the Agency will not be able to conclude ECAs within 12 months of the date of the HAPs proposal.

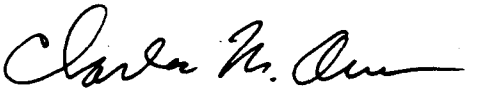
The documents submitted by the HAP Task Force went beyond PK by including an alternate testing strategy for each chemical to respond to the proposed testing identified in the proposed HAPs test rule. EPA's evaluations of these proposals identify changes or additions that provide for testing of EDC and TCE as an alternative to the testing contained in the proposed HAPs test rule. If this testing is incorporated into ECAs that are successfully concluded between EPA and the HAP Task Force, and if the data resulting from testing under the ECAs are acceptable to the Agency, such testing will provide an alternative to some or all of the testing proposed for EDC and TCE in the HAPs test rule. If testing under these ECAs does not fulfill the Agency's needs, EPA reserves the right to meet these needs through rulemaking.

EPA notes that the HAP Task Force makes certain assumptions regarding the interpretation and use of the available toxicological database for chemicals with similar physicochemical characteristics as EDC and TCE. The testing requirements for EDC and TCE in the proposed HAPs test rule were identified by EPA for the purpose of providing a database to permit the assessment of residual risk following the implementation of the maximum achievable control technology (MACT) standards required by the Clean Air Act. EPA must apply rigorous standards to determine the adequacy of studies to be used for route-to-route extrapolation. Although, as stated earlier in this letter, EPA considers its current analysis of the studies cited in the EDC and TCE PK Proposals to be preliminary, the Agency will be prepared to discuss all issues in detail with the members of the HAP Task Force if the Agency decides to proceed with the ECA process.

It is important that member companies of the HAP Task Force recognize the importance of responding to the request for comments on the proposed HAPs rule. The submission of PK proposals to develop ECAs to conduct testing alternative to that contained in the HAPs test rule is no guarantee that EPA and the HAP Task Force will, in fact, conclude such agreements. Therefore, I urge the companies to submit comments on the proposed HAPs rule as an activity separate from the ECA process. Please submit three copies of written comments on the proposed HAPs test rule, identified by document control number (OPPTS-42187A; FRL-4869-1) to: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Document Control Office (7407), Rm. G-099, 401 M St., SW, Washington, DC 20460.

In sum, EPA would like to thank the HAP Task Force for its initial proposals. If you have any technical questions about EPA's comments on your proposals, please contact Annie Jarabek at (919) 541-4847 (voice), (919) 541-1818 (fax), or jarabek.annie@epamail.epa.gov (e-mail). For questions about the ECA process, please contact Richard Leukroth at (202) 260-0321 (voice), (202) 260-8850 (fax), or leukroth.rich@epamail.epa.gov (email).

Sincerely,



Charles M. Auer
Director
Chemical Control Division

Enclosures

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Preliminary EPA Technical Analysis of Proposed Industry Pharmacokinetics (PK) Strategy for 1,1,2-Trichloroethane

June, 1997

Chemical Name:	1,1,2-Trichloroethane
CAS No.: 79-00-5	**Molecular Weight:** 133.41
Vapor Pressure: 19 torr at 20°C	**Chemical Formula:** $C_2H_3Cl_3$
PK Proposal Submitted by:	The HAP Task Force, dated November 22, 1996, and entitled: "Proposal for Pharmacokinetics Study of 1,1,2-Trichloroethane."

Contains No CBI

Preliminary EPA Technical Analysis of Proposed Industry Pharmacokinetics (PK) Strategy for 1,1,2-Trichloroethane

(1) Introduction

EPA is providing the following preliminary technical analysis and suggestions in response to a proposal by the HAP Task Force for conducting pharmacokinetics (PK) studies and additional toxicity testing on 1,1,2-trichloroethane (1,1,2-TCE). This proposal was prepared in response to EPA's invitation for proposals for pharmacokinetics (PK) studies for the hazardous air pollutants (HAPs) listed in the proposed test rule for HAPs (61 FR 33178; June 26, 1996). The PK studies would be used to inform the Agency about route-to-route extrapolation of toxicity data from routes other than inhalation when it is scientifically defensible to empirically derive the inhalation risk. The PK proposals could form the basis for negotiation of enforceable consent agreements (ECAs) that would provide for testing in lieu of some or all of the tests proposed in the HAPs rule. (The procedures for ECA negotiations are described at 40 CFR 790.22(b).) Accordingly, this analysis, including all discussions concerning data adequacy and test procedures/methods pertains only to the adequacy of the PK proposal for its intended purpose and not to the statutory basis for issuing the HAPs rule under section 4 of the Toxic Substances Control Act (TSCA).

Pharmacokinetics and mechanistic data may be used to inform the Agency about route-to-route extrapolation when EPA determines that extrapolation from existing studies may provide sufficient data to substitute for required testing under the proposed rule. Pharmacokinetics and mechanistic data alone may not be used to substitute for proposed required testing where studies by a route other than inhalation do not exist or are deemed by EPA to be inadequate. In such cases, however, pharmacokinetics and mechanistic data may be used to support a decision that required testing could be conducted using routes other than inhalation.

EPA acknowledges that if an ECA is successfully concluded between the Agency and the Panel that provides for PK studies and other testing and if the data resulting from testing under the ECA are acceptable to the Agency, such testing will provide an alternative to some or all of the testing proposed for this substance in the HAPs test rule. If testing under the ECA does not fulfill the Agency's needs, EPA reserves the right to meet these needs through rulemaking.

(2) Toxicokinetic Properties

1,1,2-Trichloroethane (1,1,2-TCE) is slightly soluble in water. 1,1,2-Trichloroethane is a central

nervous system (CNS) depressant causing narcosis, and narcotic concentrations of this chemical also produce ocular and upper respiratory (URT) irritation. 1,1,2-Trichloroethane is rapidly absorbed, widely distributed with a tendency for higher concentrations in adipose tissue, and extensively metabolized. There is likely to be a first-pass metabolic effect in the liver following oral administrations. The limited available toxicology data suggest liver and kidney are also remote target sites. The threshold limit value - time weight average (TLV-TWA) for 1,1,2-TCE is 10 ppm (55 mg/m^3) (ACGIH, 1992).

Metabolism of 1,1,2-TCE to reactive metabolites may occur via two potential pathways: (1) oxidative metabolism via P-450 to chloroacetic acid and free radicals and reductive metabolism to acyl chlorides, or (2) reaction of parent or metabolites with glutathione to give rise to glutathione episulfonium ion, a reactive intermediate implicated in the toxicity of chemicals such as 1,2-dichloroethane. Reductive dechlorination to free radical by P-450 is believed not to be applicable to the respiratory tract due to the requirement for low oxygen content, a condition that is not likely in this tissue. Radio-labeling of the chemical results in activity covalently bound to DNA, RNA, and protein in the liver, kidney, lung, and stomach. *In vitro* studies demonstrate that the binding of the radio-label is decreased by the addition of glutathione, suggesting that the P-450 mediated metabolism is the primary activating pathway for metabolites to bind to these macromolecules.

EPA considers that, although the solubility and reactivity characteristics of 1,1,2-TCE, support the designation of 1,1,2-TCE as a Category 3 gas according to the RfC methods scheme (U.S. EPA, 1994), the limited available toxicity data are insufficient to inform this designation unequivocally. Typically, a minimum of a 90-day inhalation data base is required to adequately characterize respiratory tract effects. The potential for portal-of-entry effects has not been adequately characterized, nor has the potential for modulation of internal dose via this portal. It is possible that 1,1,2-TCE could be classified as a Category 2 gas if sufficient respiratory tract toxicity information were available, since the boundaries between categories are not discrete but based on a continuum. Both Category 2 and 3 gases require description of the disposition to remote sites.

(3) Proposed HAP Task Force PK Strategy for 1,1,2-TCE

This section describes the key aspects of the proposed PK strategy entitled: "Proposal for Pharmacokinetics Study of 1,1,2-Trichloroethane" submitted by the HAP Task Force.

A physiologically based pharmacokinetics (PBPK) model was previously developed to describe dosimetry of inhaled 1,1,2-TCE in rats (Gargas et al., 1989; 1990). The HAP Task Force proposed to validate this model with additional blood concentration-time course data on the parent compound during and following 4-6 hour inhalation exposures at several inhaled concentrations. The HAP Task Force proposed to develop an oral rat model and validate it using new experimental data. In addition, the Task Force proposed to develop a PBPK model for the

mouse and validate it based on new data using the exhaled breath technique to determine metabolic constants and vial equilibration to determine blood:air partition coefficients. Rat tissue partition coefficients will be used to estimate tissue:blood coefficients for the mouse as done previously for other chemicals.

The HAP Task Force proposed the PBPK model to perform oral-to-inhalation extrapolation of existing oral data to fulfill specific testing needs for subchronic, neurotoxicity, immunotoxicity, and carcinogenicity. Limited inhalation studies were proposed to address acute toxicity and to determine the needed blood concentration-time course data. The HAP Task Force offered weight-of-evidence arguments based on data for structurally analogous compounds as the rationale for not performing the proposed reproductive and developmental toxicity testing. Additionally, maternal toxicity at a NOAEL for developmental effects from the Seidenberg et al. (1986) study was cited as a reason not to test higher doses for developmental endpoints. The need for reproductive testing was also discounted based on the assertion by the HAP Task Force that: 1) the chemical structure shows no concern for endocrine system modulation for potential reproductive effects; 2) indirect action on reproductive behavior through CNS effects is unlikely since only anesthesia was observed at high concentrations; and 3) direct action on reproductive tissues is unlikely due to lack the of evidence concerning histopathology of 78-week studies in mice and rats (NCI, 1978). New data (Mazzulo et al., 1986; Doherty et al., 1996) on genotoxicity and cytogenicity were discussed and proposed to obviate additional cytogenicity testing.

The HAP Task Force asserted that the rapid onset of CNS symptoms suggests the appropriate dose metric for acute neurotoxic effects is the parent compound and that this is similar to other Category 3 gases (i.e., other volatile organic compounds (VOCs), that exhibit CNS effects at high concentration). In addition, they proposed that the parent compound be used as the dose metric for the immunologic effects and that the total amount metabolized in a 24-hour period be used as the internal dose metric for hepatic and other remote effects.

Table 1 compares the testing provisions described in the proposed HAPs test rule with the PK proposal submitted by the HAP Task Force. This table also summarizes EPA's preliminary response to the HAP Task Force PK proposal. Detailed discussion of EPA's preliminary technical analysis are presented in section 4 of this preliminary technical analysis.

TABLE 1. Summary Comparing Proposed Testing Provisions for 1,1,2-TCE

Testing	Acute	Subchron	Neuro (A and SC)	Develop	Repro	Immuno Screen	Cancer/ Genetox
Proposed HAPs Rule	X	X	X	X	X	X	Mod[1]
HAP Task Force PK Proposal	X[a]	R[b]	R[c]	-[d]	-[e]	R[f]	R[g]
Preliminary EPA Response to PK proposal	X[1]	X[2]	X[3](R)	X[4](R)	X[5](R)	R[6]	R[7]

X Testing requirement in the proposed HAPs test rule

R Route-to-route extrapolation

Acute testing:

X[a] Gross necropsy and histopathology to be determined as part of inhalation exposures (4-6 hour exposures) performed to obtain parent blood concentration-time course data for PBPK modeling. No bronchoalveolar lavage (BAL), macrophage function or Alarie respiratory sensory irritation test included.

X[1] EPA believes that testing should follow the Agency's upcoming health effect test guideline "TSCA Acute Inhalation Toxicity with Histopathology," the acute protocol to be required in the proposed HAPs test rule. Under an acceptable ECA, the acute protocol component could be performed as part of the proposed inhalation exposures to characterize PK or as part of neurotoxicity testing if these evaluations are performed via inhalation. EPA maintains that the BAL and macrophage function assays are needed. In addition, EPA notes that the Alarie respiratory sensory irritation test (ASTM 981-84) may be superfluous under an acceptable ECA, because additional PK and mechanistic data would be obtained.

Subchronic testing:

R[b] Route-to-route extrapolation proposed to address subchronic toxicity requirement on the basis of liver effects (LOAEL and NOAEL = 384 and 44 mg/kg-day, respectively) observed in CD-1 mice from a 90-day drinking water study by White et al. (1985); and the NOAEL observed at 92 and 390 mg/kg-day, respectively in Osborne-Mendel rats and B6C3F1 mice dose at two levels via corn oil gavage for 78 weeks (NCI, 1978).

X[2] EPA believes that there are not adequate inhalation data to characterize potential portal-of-entry effects or to characterize the dose-response of effects by this exposure route and maintains that subchronic testing as required in the proposed HAPs test rule is needed.

Neurotoxicity testing (A & SC):

R[c] Route-to-route extrapolation proposed to address acute requirement based on the data of White et al. (1985) demonstrating a LOAEL and a NOAEL of 450 and 400 mg/kg-day, respectively, for sedation and loss of righting reflex. NCI (1978) data proposed to address subchronic requirement, based on lack of clinical signs and histopathology in brain.

X[3](R) EPA believes that both the acute and subchronic data needs for neurotoxicity are not adequately addressed in the HAP Task Force PK proposal given the inadequacy of the oral data proposed for extrapolation. EPA maintains that acute and subchronic neurotoxicity testing as required in the proposed HAPs test rule is needed. EPA believes that, as an alternative, these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed under an acceptable ECA.

Developmental testing:

-[d] The HAP Task Force cited the Seidenberg et al. (1986) study as a reason not to test higher doses for

developmental toxicity since a 350 mg/kg/day corn oil gavage dose was considered a NOAEL for developmental effects. In addition, the HAP Task Force offered a weight-of-evidence argument to suggest that developmental toxicity is not an issue for chlorinated ethanes based on structure activity relationship analogs (SAR).

X^4(R) EPA believes that the data needs for developmental toxicity are not adequately addressed due to the inadequacy of the oral data proposed for extrapolation. EPA maintains that developmental studies in two species are needed, as required in the proposed HAPs test rule. EPA believes that, as an alternative, these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed under an acceptable ECA.

Reproductive testing:

[e] The HAP Task Force proposed that reproductive toxicity is not a potential endpoint based on the lack of evidence in histopathology in mice and rats exposed orally via corn oil gavage (NCI, 1978) and, in addition, offered a weight-of-evidence argument based on SAR analogs to suggest reproductive toxicity is not an issue for chlorinated ethanes.

X^5(R) EPA believes that the data need for reproductive toxicity is not adequately addressed in the HAP Task Force proposal, given the inadequacy of the oral data proposed for extrapolation. EPA maintains that reproductive toxicity testing, as required in the proposed HAPs test rule, is needed. EPA believes that, as an alternative, these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed under an acceptable ECA.

Immunotoxicity screen:

R^f Route-to-route extrapolation proposed for mice data based on a LOAEL and a NOAEL of 44-46 and 3.9-4.4 mg/kg-day, respectively, for depressed humoral immunity observed in Sanders et al. (1985) and NOAEL of 390 mg/kg-day for histopathology in immunological tissues (spleen, bone marrow, lymph nodes) in NCI (1978).

R^6 EPA believes at this time that the oral data of Sanders et al. (1985) are acceptable to address the immunotoxicity data need, provided that under an acceptable ECA, quantitative route-to-route extrapolation is performed and that the immunotoxic effect that serves as the basis of the extrapolation should be the effect observed in the antibody-forming cell to sheep red blood cells (SRBC) assay.

Cancer/Genetox testing:

Mod^1 Modified cancer bioassay (one sex of each species); gene-tox *in vivo* cytogenetics

R^g The HAP Task Force proposed that cytogenicity was addressed by *in vivo* Radio labeling data of Mazzulo et al. (1986) and *in vitro* micronuclei test data of Doherty et al. (1996). Route-to-route extrapolation of NCI (1978) data on hepatocellular carcinomas in mice proposed to address cancer bioassay requirement.

R^7 EPA believes that if a quantitative route-to-route extrapolation can be developed under an acceptable ECA, then the use of the NCI (1978) data with the genotoxic assumption as its basis would allow the Agency to re-evaluate the need for the inhalation carcinogenicity bioassay.

(4) EPA Comments on the HAP Task Force Proposed PK Strategy for 1,1,2-TCE

EPA has reviewed the HAP Task Force proposal for a PK strategy to address the data needs for 1,1,2-TCE. This section provides detailed comments on the various components of the proposal. These comments include suggested changes that EPA believes should be made in order for the proposal to be found acceptable.

EPA agrees generally with the proposed strategy and believes that the use of the PBPK model to extrapolate existing oral data effect levels across routes is acceptable. However, EPA does not agree that some of the proposed oral data are adequate to use for route-to-route extrapolation of certain endpoints. In addition, EPA considers that the limited available toxicity data are insufficient to support the designation of 1,1,2-TCE as a Category 3 gas unequivocally. EPA maintains that a 90-day inhalation study (the minimum data base needed for derivation of an inhalation RfC) is needed to rule out portal-of-entry effects and to establish dosimetry of the modulation of internal dose via inhalation.

PK Model: EPA believes that the proposed development and validation of the rat and mouse PBPK models is an acceptable approach for route-to-route extrapolation. However, due to the affinity for fat tissue, sequestration in these compartments with leaching back into the blood stream during post-exposure may prevent total clearance of the compound within the post-exposure periods, especially at higher concentrations. Thus, in addition to the several concentrations proposed, EPA believes that a series of repeated exposures demonstrating that periodicity has been attained for the blood concentration time-course data is needed since the objective includes extrapolation of subchronic and chronic data. The proposed oral gavage dosing with both vehicles (corn oil and water) used in the existing toxicity studies that are the objective of the route extrapolation, is both appropriate and necessary. EPA also agrees with the HAP Task Force that if these oral uptake data are not predicted well by the use of the model developed with the proposed default values (1.0 hr^{-1} and 5.0 hr^{-1} for water and oil) for oral absorption, that a more formal measure of the rate constants will be performed. Total radio-labeled DNA/RNA/protein adducts, which have been identified as major stable biomarkers of the P-450 metabolic pathway, are strongly encouraged to evaluate metabolism adequately and to serve as a surrogate for DNA reactivity. These data will be needed if blood or tissue concentrations of the parent compound are determined to be inadequate to characterize the disposition of the chemical by each route of exposure.

EPA agrees that the parent compound is a reasonable dose metric for extrapolation of the CNS and immunologic effects, given the limited mode-of-action information. EPA also agrees with the proposed dose metrics for remote effects, but believes that information should be presented on the parent dose metrics as well to better evaluate nonlinearities introduced by metabolism.

Acute and Subchronic Toxicity testing: EPA maintains that adequate respiratory tract data are not available to characterize the lack of portal-of-entry effects or the modulation of internal dose by this entry. It should be noted that the EPA gas category scheme (U.S. EPA, 1994) was not intended to be used in the absence of toxicity data. The intent of the EPA category scheme was to aid in the development of appropriate dosimetric adjustments. PK data alone are not definitive but rather can be used to describe the time course and concentrations of target tissue dose once the toxicity and mode-of-action for a chemical are determined. There are no short-term or longer-term inhalation data that are adequate to allay concern that some potential exists for this chemical to perturb the respiratory tract or to characterize the dose-response. Some similar chemicals (e.g., toluene and styrene) have demonstrated the ability to produce lesions in the portal-of-entry, possibly via metabolism in respiratory tract tissues. Further, EPA believes that the minimum data base for inhalation RfC derivation is generally considered to be a 90-day inhalation study. Thus, EPA maintains that a 90-day inhalation study as required in the proposed HAPs test rule, is needed. EPA agrees with the proposal to perform histopathology requirements as a component associated with studies to determine blood concentration-time course or as part of acute neurotoxicity testing if such testing is performed by inhalation exposures (see below). EPA also maintains that the BAL and macrophage function assays are needed. EPA believes that these assays can be readily addressed as satellite assays to other proposed studies. EPA notes that the Alarie respiratory sensory irritation test (ASTM 981-84) may be superfluous under an acceptable ECA, because additional PK and mechanistic data would be obtained.

Neurotoxicity testing: EPA maintains that the neurotoxicity data need is not adequately addressed in the HAP Task Force PK proposal due to the inadequacy of the oral data proposed for extrapolation. The NCI (1978) and the White et al. (1985) studies on 1,1,2-trichloroethane included only clinical observations and non-perfusion based histopathology. These studies also lack any systematic attempt to quantify exposure-related changes in behavior as is required by EPA in its neurotoxicity testing guidelines. Therefore, EPA believes that both acute and subchronic neurotoxicity testing is needed to evaluate residual risk and other purposes. EPA believes that, as an alternative, these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed under an acceptable ECA. EPA believes that concern for greater parent compound delivery to the CNS, due to the anticipated lack of a first-pass effect in the liver for a portion of the inhaled dose, should be addressed by reporting parent and metabolite blood and CNS time-course data by both oral and inhalation routes in the PK studies.

Developmental Toxicity testing: EPA regards the data presented by Seidenberg et al. (1986) and the table entitled "Summary of Developmental Data for Chlorinated Ethanes" on pages 14 and 15 of the HAP Task Force PK proposal as inadequate to characterize the developmental toxicity of 1,1,2-TCE. The Seidenberg et al. (1986) and Seidenberg and Becker (1987) investigations used a screening assay for developmental toxicity in mice that does not include internal evaluations for malformations. Furthermore, the developmental period of exposure did not cover the entire period of major organogenesis (i.e., 6-15 days). EPA has several additional concerns with the

HAP Task Force summary table "weight-of-the-evidence" argument that chlorinated ethanes, in general, are not a concern for developmental effects. The table limits effects to malformations and does not include other important manifestations of developmental toxicity (e.g., resorptions or dead implants). Also, EPA considers that a few studies are inadequate evaluations since exposure dosing did not occur for the entire gestation period. EPA does not agree with the conclusion stated in the table that the Payan et al. (1995) assessment of 1,2-dichloroethane is "negative." EPA notes that this study shows a dose-trend for an increase in the frequency of resorptions and dead implants which are considered a significant effect by the Agency. Finally, the table does not provide adequate information about the number of animals evaluated or if an adequate dosing regimen was used for each of the studies tabulated. Given these insufficiencies, there may be other deficiencies in the studies shown in the table. Thus, EPA maintains that developmental toxicity studies in two species are needed. EPA believes that, as an alternative, these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed under an acceptable ECA.

Reproductive Toxicity testing: EPA regards the NCI (1978) bioassays as insufficient to characterize the reproductive toxicity of 1,1,2-TCE since histopathology was performed only on adult animals at the end of a chronic study. EPA maintains that a two-generation reproductive assay is needed, as required in the proposed HAPs test rule, to adequately assess reproductive capacity. The HAP Task Force argument that chlorinated ethanes in general are not a concern for reproductive toxicity, based on their summary table (see pages 17 and 18 of the PK proposal), is also not acceptable to EPA based on similar concerns for the summary information as expressed above under the Developmental Toxicity section. For example, the Lane et al. (1982) study does not meet the requirements for a two-generation reproductive study as the offspring generation animals were not evaluated adequately, nor was histopathology performed. Further, perchloroethylene (C_2Cl_4) was not considered as part of this analysis. EPA notes that perchloroethylene (PCE) is a known cause of human reproductive effects (Eskenazi, et al. 1991) Also, all four possible trihalomethanes containing bromine and chlorine, as well as PCE have recently been demonstrated to produce a decrease in serum testosterone levels (Potter et al. 1996). Finally, because the neurotoxic effects have not been adequately characterized, the potential for indirect action on reproductive behavior can not be ruled out as proposed. In summary, EPA maintains that reproductive toxicity testing by the inhalation route is needed. EPA believes that, as an alternative, these studies could be performed via the oral route, if quantitative route-to-route extrapolation can be developed under an acceptable ECA.

Immunotoxicity screen: EPA agrees at this time that the oral data of Sanders et al. (1985) are acceptable to address the immunotoxicity data gap, but believes that the effect used as the basis of the route-to-route extrapolation is the effect in the antibody-forming cell to sheep red blood cells (SRBC) assay and not the serum hemagglutinin antibody titers. EPA notes that typically a decrease in the SRBC assay is indicative of an effect (immune suppression). This study shows a transient but significant increase which is difficult to interpret, but since the increase is about equal to that shown in Table 16 of the White et al. (1985) study, EPA believes that there is no suppression of the antibody response to SRBC at the dose levels tested in Sanders et al. (1985).

Carcinogenicity/Genetox testing:

EPA agrees at this time with the proposal to designate 1,1,2-TCE as genotoxic on the basis of the DNA, RNA, and protein binding demonstrated by the Radio labeling studies (Mazzulo et al., 1986). Since these same data suggest that mice are more susceptible than rats, and because corn oil gavage may exacerbate dose-rate effects on metabolism, EPA believes that if a quantitative route-to-route extrapolation can be developed under an acceptable ECA, then the use of the NCI (1978) data with the genotoxic assumption as its basis would allow the Agency to re-evaluate the need for the inhalation carcinogenicity bioassay. In addition, EPA believes at this time that the new data of Doherty et al. (1996) adequately address the issue of cytogenicity such that additional testing for *in vivo* cytogenetic testing should be considered superfluous.

(5) References

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(6) PK Proposal Review Staff

The following table lists individuals who contributed in the preparation of EPA's preliminary technical analysis of the HAP Task Force PK proposal for 1,1,2-trichloroethane (1,1,2-TCE).

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